REMARKS

The amendment to claim 42 finds support at page 6 lines 17 - 19 of the specification and makes clearer the effect being obtained..

For convenience, the main points made in this response are summarized as follows:

1. Formulation

Those skilled in the art would have no difficulty in using standard techniques referred to in the application to produce compositions as specified in the claims. This application has been under prosecution for seven years and hitherto no examiner has doubted that the specification provides an enabling disclosure.

2. University of Rochester vs Searle

Holds that when claiming a method of use, it was insufficient to show possession of the invention that one merely had an idea as to how suitable compounds might be identified but had not identified any such compounds and those skilled in the art could not identify such compounds. That is not the case here. Those skilled in the art had ample knowledge of how to produce formulations that delayed release of active compounds. What they did not have prior to the present invention was any reason to apply such knowledge to the active compounds specified in the claims.

3. University of California vs Lilly

Holds that one function of the written description requirement is to show that the inventor had invented what is claimed before the application was filed, or in other words had possession of that invention at that time. The invention here running through all of the claims is the combination of use of drugs of a particular half life and avoidance of release of drug at particular times so as to permit acetycholinesterase activity during periods of sleep. This is clearly set out in the application as filed.

4. Psychotropic drugs as discussed by Conte

Cholinesterase inhibitors were not considered conventional psychotropic drugs by Conte. As listed by the PDR, psychotropic drugs included antianxiety agents, hypnotics, mood tabilizers (antimanic drugs), antipsychotic and antidepressant drugs. The cholinesterase inhibitors were antidementia or cognitive enhancing drugs with unique psychotropic effects in Alzheimer's disease (AD). An unqualified reference to psychotropic drugs in 1998 was not likely to have been considered to include Alzheimer drugs.

5. Medicating an Alzheimer patient during sleep

The art actively chose to medicate AD patients during sleep. Fluctuations in the level of acetylcholinesterase inhibition were thought to be responsible for nausea and vomiting, the leading side effects and reason for discontinuing the cholinesterase inhibitors. The good tolerability of drugs that acted throughout the 24 hour period was

attributed to their irreversibility or very long half life, and a shorter-acting cholinesterase inhibitor was recently reformulated into a 24 hour patch.

6. Treatment of the circadian rhythm itself

Conte wanted to treat diseases whose activity was secondary to an endogenous circadian rhythm. The present application describes a method to change the circadian rhythm itself, noting that it was abnormal in Alzheimer's disease. As noted at page 6 lines 18 - 19: "An additional potential utility of a dosage form which can be taken when convenient, and active when needed, would therefore be the superimposition of a physiological rhythm of cholinergic activity, via a dosage formulation, onto a brain in which the cholinergic system is deteriorating." Alzheimer patients were known to have disrupted circadian rhythms. A number of treatments had been tried with variable success. The disclosure proposed direct treatment of the deteriorated circadian rhythm in Alzheimer disease patients.

7. *Unexpected results*

Currently the most common treatment for Alzheimer's disease is with the drug donepezil. Donepezil has a half life of 70 hours, much longer tham the maximum half life permitted in the present invention. The central nervous system (CNS), as expected, produces a substantial counterregulatory increase in acetylcholinesterase (AChE) during donepezil therapy. Animal studies suggest that one potential explanation for this is unphysiologic cholinergic stimulation during the rest period. This increased AChE is likely responsible for decreases in the donepezil therapeutic effect with continued treatment. . In an attempt to overcome the clinical deterioration in patients who remain on donepezil, studies are now being conducted at more than twice the previous maximum dose. Galantamine, surprisingly, has a more modest AChE stimulation, and less long-term cognitive deterioration.

8. *Twilight sleep*

This is a condition induced by scopolamine used in the past for sedation and the induction of amnesia for pain during labor and childbirth. It has nothing to do with regular sleep.

We will now consider the issues in more detail.

In response to the rejection under 35 USC 112, paragraph 2, Claim 40 has been amended to replace the tradenames Probanthine and Robinul by their generic names.

Turning now, to the question of whether the written description requirement of 35 USC 112, paragraph 1, has been met, it seems strange that this is being raised now for the first time. This application was filed in 2001 and has been subject to extensive prosecution in which the description was seemingly accepted as being adequate. Be that as it may, however, as the examiner notes, the requirement is met if on the facts of the application one skilled in the art would have known what structure, material or acts perform the" function in question. The specification at page 7 starting at line 20 states that formulations according to the invention can be obtained by use of the information set out in the text "Sustained Release Medications" by J.C. Johnson,

Noyes Data Corporation 1980 or by the Conte reference cited in the present action in the context of a 35 USC 103 rejection. The examiner has given no reason to doubt that following one of these teachings it is possible to formulate a drug dosage having the properties defined in the claims. The drug formulation art is a well developed one. Once told what release parameters to aim for those skilled in the art have, and at the date of the invention would have had, no difficulty in producing a suitable formulation.

The examiner refers to *University of Rochester v. Searle*. This is indeed a key case on the law on written description. The fact of that case are, however, totally different from the present situation. In that case, the claim in question was as follows:

> A method for selectively inhibiting COX-2 activity in a human host, comprising administering a non-steroidal compound that selectively inhibits activity of the COX-2 gene product to a human host in need of such treatment.

No suitable compounds were named in the specification because none were known – not even to the inventors. Identification of actual compounds that would meet the definition occurred only after the patent application had been filed. Not surprisingly it was found that the inventors did not have possession of the invention at the time of filing. There was no one skilled in the art to tell what compounds had the defined property because no one had yet identified any such compounds. What had been achieved was indeed as noted by the examiner a plan for an invention rather the invention itself.

This is not the case here.

Unlike the unknown compounds in the *University of Rochester* case, the nature and amount of suitable excipients for use in the present invention can readily be determined by those skilled in the art. This is in effect accepted by the examiner since no issue is raised as to whether the present specification contains an enabling disclosure. If there is sufficient of a description to enable one skilled in the art to put the invention actually described in the specification into practice, there is sufficient description to meet the written description requirement.

The examiner quotes from *University of California v. Eli Lilly*, but leaves out key language. The full passage from which the Examiner's quotation is taken reads as follows:

> An adequate description of a DNA, such as cDNA of the recombinant plasmids and microorganisms of '525 patent requires a precise definition, such as by structure, formula, chemical name or physical properties, not a mere wish or plan for obtaining the claimed chemical invention. 43 USPQ2d 1398 at 1404.

The issue in this case was whether a description of rat cDNA was sufficient of a written description for a claim to a procaryotic microorganism containing "a nucleotide sequence having the reverse transcript of an mRNA of a [human] , which mRNA encodes insulin". As noted in the paragraph preceding that referred to by the examiner, it is stated that the

purpose of the written description requirement is to enable those skilled in the art to be able to conclude that "the inventor invented the claimed invention". The decision when read as a whole makes it clear that where there is unpredictability, more may be required of the applicant than in more traditional circumstances.

In the present case, however, we are not dealing with materials having unpredictable properties. The examiner's position seems to be that possession of an invention requires detailed description of what is already known in the prior art or else actual reduction to practice. This is not the law. The specification is written for those skilled in that art. The writer of the specification is entitled to rely on the skilled reader applying his or her own knowledge to what is described. In unpredictable arts such as DNA at the time of the *University of California invention* or in devising a whole new approach to pain control in the case of the *University of Rochester* invention, the skilled person has little relevant knowledge and so the writer of the patent application must provide more than is the case where the skilled worker already has tools at hand that will enable him or her to produce what is set out in the claims based on the direction given in the specification.

It is therefore submitted that the requirements of 35 USC 112 have been met.

Turning now to the rejection under 35 USC 103, the Office Action states that "in the absence of a showing of unexpected results commensurate in scope with the claims, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to formulate galanthamine or galanthamine-analogues as instantly claimed into compositions providing delayed release of the active agent for use in the treatment of Alzheimer's disease. The skilled artisan would have been motivated to do so because Conte *et al* teach that psychotropic active drugs are agents having significant daily variations in pharmacokinetics and/or drug effects depending on physiological and/or physiopathological changes of circadian rhythmicity." (page 12, paragraph 2). Conte does not use the phrase "psychotropic active drugs." The phrase he does use reads "antiasthmatic, antihistaminic, psychotropic, anaesthetic, cardiovascular active drugs, NSAIDs, etc." The adjective "active" modifies "cardiovascular" as the words antiasthmatic, antihistaminic and anesthetic would not be followed by "active" in normal usage, and there is yet another drug class, NSAIDs, following "cardiovascular active." Thus, Conte is referring to classes of drugs, not to properties which a drug might possess. The psychotropic drug category, defined by the examiner as "a chemical substance that acts primarily upon the central nervous system where it alters brain function" (page 13 footnote) may be interpreted to include the antidementia drugs. However, that definition of psychotropics also embraces anesthetics (as well as narcotics, antiepileptics, anti-Parkinson agents, etc), which are referred to by Conte as a separate class. Therefore, it appears that Conte was referring to a more limited class of drugs than everything having CNS activity and altering brain function.. At the time of the Conte article, the term "psychotropic" was in fact widely used as having a narrower meaning and it seems that Conte in fact meant when referring to "psychotopic" drugs to refer to such conventional psychotropic drugs. Indeed, the PDR for 1998[1] specifies those drugs usually classified as psychotropic.1 Its listing of psychotherapeutic drugs, which specifies an alternate name of psychotropic drugs, includes antianxiety agents, hypnotics, mood stabilizers (antimanic drugs), antipsychotic and antidepressant drugs. Alzheimer drugs are not

[1] Physicians' Desk Reference, 52" Edition, 1998; Product Category Index Quick Reference Guide and Product Category Index

included in this and are categorized and alphabetized by themselves. The situation has not changed. The 2008 PDR handles these terms the same way.[2]

Publications by those in the art around the time of the priority date hoped that the cholinesterase inhibitors would have useful behavioral effects in Alzheimer patients, but differentiated them from conventional psychotropic agents. Tariot et al, discussing agitation in dementia, noted that "when psychotropic medications are used, they should be used judiciously, in the lowest effective doses and for the shortest period of time necessary."[3] This does not describe the use of cholinesterase inhibitors, which were dosed as high as tolerated, and given chronically. Similarly, Devenand reviewed classic psychotropic agent use in dementia and recommended low doses and attempts to "taper or discontinue the psychotropic medication," which would certainly not characterize the use of the antidementia drugs.[4] Jacobsen and Comas-Diaz experimented with donepezil for the "treatment of psychotropic-induced memory loss, dry mouth and constipation,"[5] In these reports, the Alzheimer drugs were not indicated to be psychotropic medications. However, it was beginning to be appreciated that cholinergic augmentation strategies might ameliorate the behavioral as well as the cognitive problems in Alzheimer patients. Thus Cummings, who taught that "Neuropsychiatric symptoms are also common in Alzheimer's disease and may be ameliorated by conventional psychotropic agents," also noted that "Cholinergic compounds are unique psychotropic agents that exhibit disease specificity, exerting beneficial effects only in diseases such as AD with cholinergic deficits".[6 7 8] Therefore the Alzheimer drugs were not regarded as conventional psychotropic agents, but when additional explanations were provided, could be considered as having unique psychotropic properties.

Thus, the unqualified listing in Conte is not likely to have been understood as including cholinesterase inhibitors in 1998.

The examiner goes on to consider that dementias "related" to Alzheimer's disease as referred to in WO 88108708 must include conditions treated by psychotropic drugs, This is incorrect. As noted above in the context of Conte's use of the word "psychotropic" , the word "psychotropic," in 1998, did not connote Alzheimer's disease therapy. Therefore there is no reason why one skilled in the art would have combined Conte and *WO* 88108708 as was done by the examiner.

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[2] Physicians Desk Reference, 62" Edition, 2008, Product Category Index, Quick Reference Guide and Product Category Index

[3] Tariot P, Gaile SE, Castelli NA, Porsteinsson **AP**, Treatment of agitation in dementia. New Dir Ment Health Serv 1997; 76: 109-23

[4] Devanand DP, Behavioral complications and their treatment in Alzheimer's disease, Geriatrics 1997; 52:Suppl 2:S37-39

[5] Jacobsen FM and Comas-Dias L, Donepezil for psychotropic-induced memory loss, J Clin Psychiatry 1999 Oct;60(10):698-704

[6] CummingsJ L, Mendez MF, Alzheimer's disease: cognitive and behavioral pharmacotherapy. Conn Med 1997; 61:543-552

[7] Cummings JL, Changes in neuropsychiatric symptoms as outcome measures in clinical trials with cholinergic therapies for Alzheimer disease. Alzheimer Dis Assoc Disord 1997; 11 Suppl 4:Sl-9

[8] Cummings JL, Back C, The cholinergic hypothesis of neuropsychiatric symptoms in Alzheimer's disease. Am J Geriatr Psychiatry 1998; 6(2Suppl 1):S64-78

The Office Action states "Further, one of ordinary skill in the art would recognize that a patient being treated for Alzheimer's or other dementia would not be in need of medication while they are sleeping. (page 11, paragraph 1) This statement is incorrect and does not describe the preferred periods of cholinesterase inhibitor activity in 1998 nor even today. For practical reasons, the art preferred a continuously-acting cholinesterase inhibitor to one which worked only during the day because of a lower incidence of side effects such as nausea and vomiting. In explaining the good tolerability of metrifonate, an irreversible cholinesterase inhibitor, Schmidt and Henig state, "The incidence of drug-related cholinergic adverse events is related to the rate of change in cholinergic transmission, rather than to the achieved level of cholinesterase inhibition . As the greatest rate of change in cholinergic transmission occurs during the transition from baseline to peak enzyme inhibition, it is, therefore, beneficial to maintain inhibition for as long as possible."[9] A drug that is active only during the day of necessity must go from baseline to peak inhibition every morning, which was understood to be a cause of the most common reasons for drug discontinuation, nausea and vomiting.

Metrifonate and donepezil are drugs which produce continuous cholinesterase inhibition and this was thought to account for their tolerability. Since its launch in 1996, donepezil is the most widely prescribed drug for the treatment of Alzheimeer's disease 'Within the class of acetylcholinesterase inhibitors, metrifonate has a favourable tolerability profile that can be explained primarily by its smooth onset of acetylcholinesterase inhibition.. .In addition, metrifonate's long duration of action ensures that predictable steady-state levels of cholinesterase inhibition are achieved and maintained without clinically relevant fluctuations in enzyme activity on a day-to-day basis."[10]

A donepezil study concluded

> "Other cholinesterase inhibitors have also shown efficacy in treating symptoms of AD but are often accompanied by significant or intolerable dose-related cholinergic side effects that have limited many patients' ability to continue treatment.[6,9,26,29] The high frequency of side effects may be partially attributed to peripheral inhibition of ChE by some agents. However it may also be that the high rate of side effects is related to the high level of AChE inhibition necessary for positive cognitive effects and to rapid rates of fluctuation in AChE inhibition produced by these short-acting compounds. In comparison with the relatively short half-lives of some ChE inhibitors, the long half-life of donepezil (-70 hours) provides relative stability in the extent of AChE inhibition over the course of a day, which may also contribute to the relative reduction in cholinergic side effects seen with this drug."[11]

The preference for 24-hour versus daytime treatment of Alzheimer's disease using cholinesterase inhibitors continues to this day. Rivastigmine, a drug with a high incidence of nausea when given orally, has been reformulated into a 24 hour patch. "It provides smooth, continuous drug delivery, and has the potential to maintain

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[9] Schmidt BH, Heinig R, The pharmacological basis for metrifonate's favourable tolerability in the treatment of Alzheimer's disease. Dement Geriatr Cogn Disord 1998; 9(suppl2): 15-19

[10] Schmidt BH and Heinig R, ibid

[11] Rogers SL, Farlow MR, Doody RS, Mohs R, Friedhoff LT, et al, A 24-week, double-blind, placebocontrolled trial of donepezil in patients with Alzheimer's disease. Neurology 1998; 50:136-145

rivastigmine concentrations within an optimal therapeutic window while avoiding the peaks and troughs associated with oral drug delivery.. . In a 24-week study in 1195 AD patients, the rivastigmine 9.5 mg/24 h patch provided similar efficacy to the highest dose range of capsules, with approximately three-times fewer reports of nausea and vomiting. The patch may be the optimal way to treat dementia patients with rivastigmine."[12]

Thus, there is even today no recognition of the inadvisability of inhibiting acetylcholinesterase [AChE] during the night. Although the Examiner supposes that "one of ordinary skill in the art would recognize that a patient being treated for Alzheimer's or other dementia would not be in need of medication while they are sleeping," researchers in the field of cholinesterase inhibitors felt, and feel there was and is a need to administer medication while patients were sleeping. This need is based on the avoidance of fluctuations in levels of cholinesterase inhibition, and it is demonstrated for two of the three cholinesterase inhibitors. The third, galantamine, was produced in an awaketime-only formulation after the submission of this patent application.

The present invention includes the use of the specified formulations to normalize the circadian rhythm itself. This is claimed in claim 42. Conte gives examples of treating diseases which wax and wane secondary to changes in circadian rhythms, such as asthma, excess stomach acidity and hypertension. In a similar vein, the disclosure to this application comments on changes in bronchial reacti vity, presumably predisposing to asthmatic attacks, secondary to changes in the fundamental cholinergic rhythm. Conte proposes putting an antiasthmatic into a controlled delivery system to treat the asthmatic attack which is secondary to the circadian cholinergic rhythm.

But Conte does not address the notion of giving a drug to alter the circadian rhythm itself. Changing the circadian rhythm itself is a goal of this application. The disclosure reads "An additional potential utility of a dosage form which can be taken when convenient, and active when needed, would therefore be the superimposition of a physiological rhythm of cholinergic activity, via a dosage formulation, onto a brain in which the cholinergic system is deteriorating."

The present application at page 6 lines 7 – 13 explains that "Animals who are made hypocholinergic either by disruption of the high affinity choline uptake system or by being raised on a false cholinergic neurotransmitter have a reduced circadian variation of acetylcholine and a disrupted diurnal rhythm of locomotor activity, which correlates with the cholinergic hypoactivity. (Morley 1989, Szyrnusiak 1993) This same situation exists in Alzheimer patients who have both cholinergic deficits and disruption of normal sleep-wake cycles."

It was understood in 1998 that Alzheimer's disease caused deterioration of circadian rhythms and of the circadian rhythm generator, the suprachiasmatic nucleus. Witting, Kwa et al noted, "The suprachiasmatic nucleus, considered to be the endogenous circadian clock in the mammalian brain, shows morphological changes with aging,

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[12] Cumrnings J, Winblad B, A rivastigmine patch for the treatment of Alzheimer's disease and Parkinson's disease dementia. Expert Rev Neurother 2007; 7: 1457-63

which become even more pronounced in Alzheimer's disease." They assessed the rest-activity rhythm of normal subjects and Alzheimer patients and noted that the "rest-activity rhythm was markedly disturbed in many of the AD patients and tended to be correlated with the severity of the dementia."[13]

Tate et al introduced Alzheimer neuropathology into the suprachiasmatic nucleus of the rat by grafting cells producing the toxic peptide, beta amyloid. This resulted in disruption of the circadian pattern, including overactivity during the rest phase, as seen in Alzheimer patients. Tate et al state

> "Alzheirner patients exhibit irregularities in the patterns of normally circadian (daily) rhythms. Alzheimer-type pathology has been reported in the hypothalamus and in the suprachiasmatic nuclei, the putative site of the circadian oscillator. We examined the relationship between the neuropathology of Alzheimer disease, as modeled by an animal system, in circadian dysregulation by grafting genetically transformed calls that overexpress beta A4 amyloid into the suprachiasmatic nuclei of adult rats. Grafts of beta A4 positive cells, but not of control cells, significantly altered the pattern of activity of implanted rats. Although experimental conditions included light-dark cycles that normally tend to drive rats to 24-h rhythms, animals with grafts of beta A4 positive cells showed abnormally high levels of activity during the light phase *[the rest period in a rat]* in addition to a disrupted circadian pattern.. .These data indicate that disruption of circadian activity is a behavioral measure of the consequences of beta A4 accumulation in brain implants."[14]

The circadian rhythm deterioration was specific to Alzheimer's disease. Mishima et al studied a group of Alzheimer and multi-infarct dementia patients and found that the percentage of nighttime activity correlated with the degree of dementia only in the Alzheimer group. They commented "The different properties of the biological rhythm disorders among the SDAT and MID groups possibly underly their sleep and behavioral disorder.[15]

There have been many attempts to fix the disrupted circadian rhythm in Alzheimer's disease. Van Someren, Scherder and Swaab applied transcutaneous electrical nerve stimulation in the hope of stimulating direct and indirect spinal projections to the suprachiasmatic nucleus.[16] Satlin et al attempted to improve circadian rhythmicity, including nighttime activity, with bright light treatment. [17] [18]

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[13] Witting W, Kwa IH,Eikelenbloom P, Mirrniran M, Swaab DF, Alterations in the circadian rest-activity rhythm in aging and Alzheimer's disease. Biol Psychiatry 1990; *7563-72*

[14] Tate B, Aboody-Guterman KS, Morris AM, Walcott EC, Majocha RE, Marotta CA, Disruption of circadian regulation by brain grafts that overexpress Alzheimer betalA4 amyloid. Proc Natl Acad Sci USA 1992;89:7090-4

[15] Mishirna K, Okawa M, Satoh K, Shimizu T, Hozumi S, Hishikawa Y, Different manifestations of circadian rhythms in senile dementia of the Alzheimer type and multi-infarct dementia. Neurobiol Aging 1997; 18:105-9

[16] Van Someren EJ, Scherder EJ, Swaab DF, Transcutaneous electrical nerve stimulation (TENS) improves circadian rhythm disturbances in Alzheimer disease. Alzheirner Dis Assoc Disord 1998; 12: 114-8

[17] Satlin A, Volicer L, Ross V, Herz L, Campbell S, Bright light treatment of behavioral and sleep disturbances in patients with Alzheimer's disease. Am J Psychiatry 1992; 149: 1028-32

Similarly, Van Someren et al noted "circadian rhythm disturbances in patients with Alzheimer's disease.. .manifest themselves through a fragmentation of the rhythm, a weak coupling with Zeitgebers and high levels of activity during the night." They concluded that "stability of the rest-activity rhythm is associated with high levels of daytime activity and high levels of environmental light" and that fragmentation of the rhythm was associated with low levels of daytime activity, especially prominent in moderately severe dementia.[19]

Deterioration of the circadian rhythm in Alzheimer's disease was widely recognized and studied prior to 1998. It was known that cholinergic transmission in the brain was generally reduced during rest periods, and elevated during waking and activity. It was known that acetylcholine injected into the brain stimulated activity and that its release was suppressed during sleep.[20] It was known that cholinergic stimulation interfered with sleep.[21] In 1974, Saito et al wrote 'These indicate that changes in the release of ACh *[acetylcholine]* may be involved in the sleep-wake cycle and daily activity rhythm of animals."[22] It was known that by reducing cholinergic activity in the brain as in Alzheimer's disease, or causing Alzheimer's neuropathology in the suprachiasmatic nucleus, one could reproduce the circadian rhythm changes seen in Alzheimer's disease.[23] [24] [25] Yet no one suggested that cholinesterase inhibitors be used to normalize the fundamental rhythm itself.

To the contrary, the notion that a cholinesterase inhibitor should be present only at a biologically appropriate time, only when endogenous acetylcholinesterase is relatively inactive, (i.e., during the day) was overridden by the marketing-driven desire to avoid fluctuations in enzyme inhibition which caused side effects, and caused patients to discontinue drug treatment. Therefore, a drug with a 70 hour half life, donepezil, was the most utilized agent. The situation has not changed. Rivastigmine, a drug with a shorter half-life, has been reformulated into a 24 hour patch.

Against this background, it can be seen that there was no reason at the time of the present invention why those skilled in the art would have thought to formulate any drug for treatment of Alzheimer's disease in such a way as to avoid activity during periods of sleep, let alone to seek to achieve this by the double requirement of

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[18] Satlin A, Volicer L, Stopa EG, Harper D, Circadian locomotor activity and core-body temperature rhythmsin Alzheimer's disease. Neurobiol Aging 1995; 16:765-71

[19] Van Someren EJ, Habebeuk EE, Lijzenga C, Scheltens P, de Rooij SE, Jonker C, Pot AM, Mirmiran M, Swaab DF, Circadian rest-activity rhythm disturbances in Alzheimer's disease. Biol Psychiatry 1996; 40:259-70

[20] Saito Y, Yamashita I, Yamazaki K, Okada F, Satorni R, Fujieda T, Circadian fluctuation of brain acetylcholine in rats. 1. On the variations in the total brain and discrete brain areas. Life Sci 1975; 16:281- 288

[21] Reimann D, Gann H, Dressing H, Muller WE, Aldenhoff JB, Influence of the cholinesterase inhibitor galanthamine hydrobromide on normal sleep. Psychiatry Res 1994; 51:253-267

[22] Saito et al. op. cit.

[23] Morley BJ, Murrin LC, AF64 depletes hypothalamic high-affinity choline uptake and disrupts the circadian rhythm of locomotor activity without altering the density of nicotinic acetylcholine receptors. Brain Res1989; 504:238-246

[24] Szymusiak R, McGinty D, Fairchild MD, Jenden DJ, Sleep-wake disturbances in an animal model of chronic cholinergic insufficiency. Brain Res 1993; 629:141-145

[25] Tate et al. op. cit.

selection of drugs having a particular half life and delay of release of drug for specified periods after administration.

The examiner points out that the presence of unexpected results may be an indicium of non-obviousness but states that the present invention has none. This is not true. ~~In~~ There was a strong motivation to use very long-acting cholinesterase inhibitors in order to improve tolerance to gastrointestinal side effects,and it was recognized that pharmacodynamic tolerance would be induced. "Pharmacodynamic tolerance refers to adaptive changes that have taken place within systems affected by the drug so that response to a given concentration of the drug is reduced."[26] However, this disadvantage was considered to be outweighed by reduction of gastrointestinal problems. Investigators studying the control of the induction of acetylcholinesterase noted "Drugs designed to activate muscarinic AChRs, including AChE inhibitors and m1 agonists, that are currently being tested in clinical trials for the treatment of Alzheimer's disease may be expected to stimulate transcription of EGR genes along with EGR-dependent target genes. *In vivo* studies are required to test whether pharmacological treatments designed to stimulate brain muscarinic AChRs increase AChE gene expression, along with AChE enzyme activity and accelerated breakdown of acetylcholine."[27]

As expected, *in vivo* studies showed that cholinesterase inhibitors increased AChE levels in the central nervous system in Alzheimer patients.[28] "The increase of AChE was higher in patients treated with donepezil than in those treated with galantamine."

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[26] O'Brien CP, in Goodman and Gilman's The Pharmacological Basis of Therapeutics, JG Hardman and LE Limbard, editors-in-chief, page 560.

[27] Von der Kammer H, Mayhaus M, Albrecht C, Enderich J, Wegner M, Nitsch RM, Muscarinic acetylcholine receptors activate expression of the *Egr* gene family of ntranscription factors. J Biol Chem 1998; 273:14538-14544

[28] Davidsson P, Blennow K, Andreasen N, Eriksson B, Minthon L, Hesse C, Differential increase in cerebrospinal fluid-acetylcholinesterase after treatment with acetylcholinesterase inhibitors in patients with Alzheimer's disease, Neuroscience Letters 2001 ; 300: 157-160

(as shown in the figure) [29]

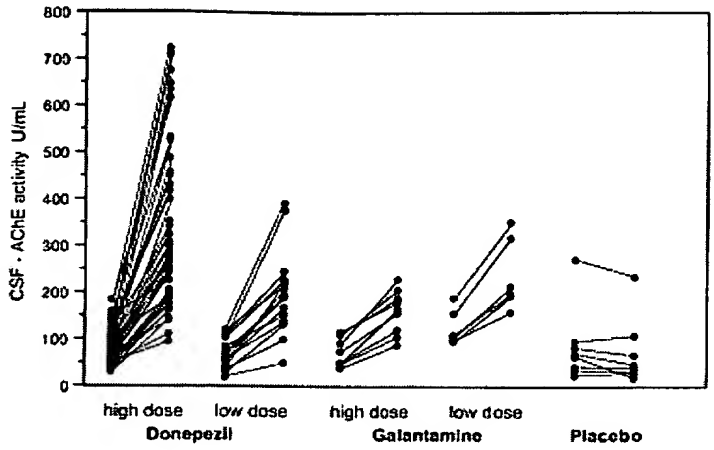


Fig. 1. CSF–AChE levels, taken before and after treatment, in a dose-dependant manner. The patients were further divided into groups receiving high or low dose. In the donepezil group, 47 patients received high dose (10 mg) and 15 patients low dose (5 mg). In the galantamine group, nine patients received high dose (32 mg) and six patients low dose (24 mg). The placebo group was composed of eight patients. The AChE assay was performed as described in the text.

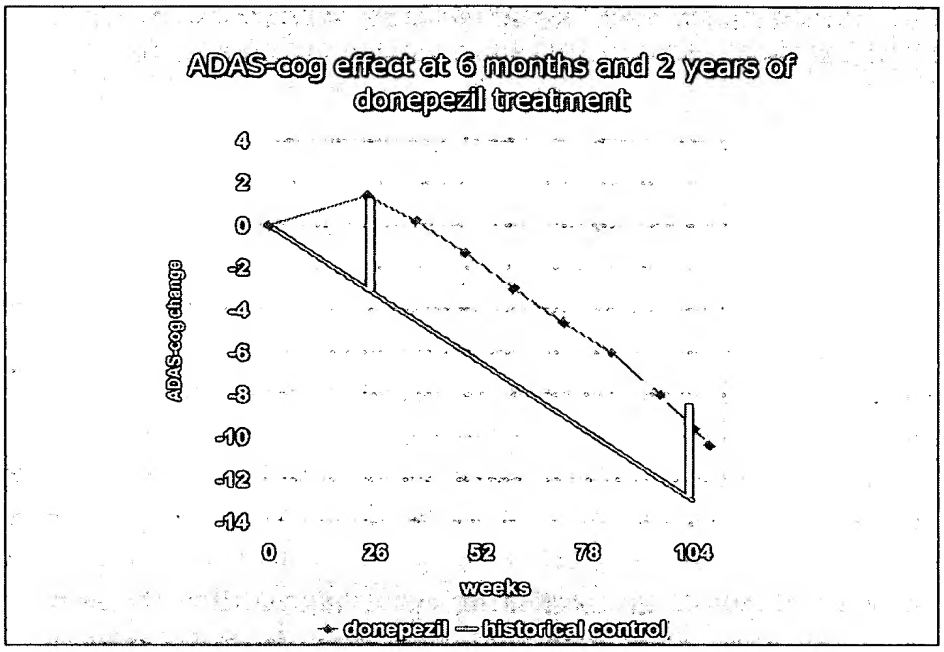
The clinical manifestation of the predicted "accelerated breakdown of acetylcholine" is a decline in the therapeutic effects of the drugs. Such declines were noted for tacrine when administerd in such a way as to try to keep levels constant.

> "A decline in improvement was measured by EEG, PET and neuropsychological testing following year(s) of tacrine treatment compared to short-term treatment (Minthon et al, 1995; Nordberg et al, 1998; Jelic et al, 1998) which raises the question of possible rebound effects and different pharmacological mechanisms following short and long-term cholinesterase inhibitor treatment. When using a quantitative EEG approach we recently observed that the AD patients treated with tacrine for 1 year showed a decrease in slow frequency (delta and theta activities) after 3 and 6 months and a decrease in fast frequency (beta) after 12 months of tacrine treatment in comparison to a matched group of untreated AD patients (Jelic et al, 1998). The long-term effect on beta EEG activity might be an early indicator of declining treatment efficiency (Jelic et al, 1998)...
>
> "Kaufer et al (1998) recently found an increased level of AChE mRNA following in vitro incubation of rat brain slices with the cholinesterase inhibitor DFP, supporting an existing feedback process of AChE following longer cholinesterase exposure....

[29] Blennow, ibid.

"The present in vivo treatment study with tacrine in AD patients revealed that such cholinesterase inhibitors, which are assumed to improve cholinergic activity in brain primarily by inhibiting AChE, may after long-term use cause an increase in brain AChE activity."[30]

In extensions of pivotal studies done in the 1990s, the therapeutic effect of donepezil, as compared to a historical control group, declined over a two-year period.[31,32]



In an attempt to overcome the reduction in the therapeutic response due to donepezil tolerance, a dose of 23 mg is now being studied, more than 2x the current maximum dose of 10 mg/day.[33]

Contrary to expectation, the diminished efficacy over time which has been shown to occur with donepezil does not occur with formulations of the present invention where the half life of the inhibitor and the manner of release are balanced to achieve periods when release of inhibitor is avoided so that periods of acetylcholinesterase activity are permitted.

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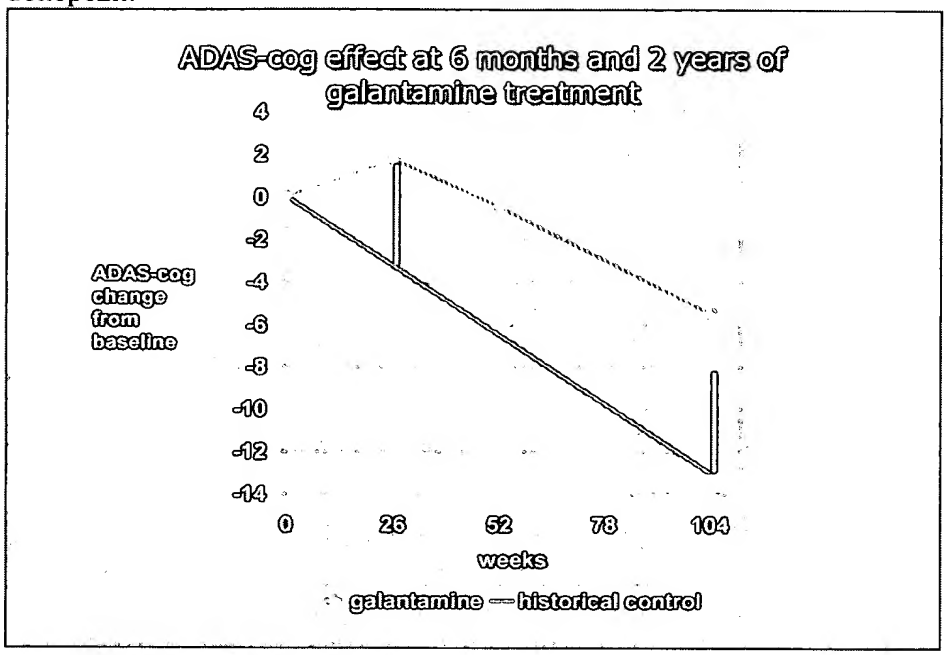
[30] Nordberg A, Hellstrom-Lindahl E, Almkvist O, Meurling L, Activity of acetylcholinesterase in CSF increases in Alzheimer's patients after treatment with tacrine. Alzheimer's Reports 1999; 2:347-352

[31] Doody RS, Geldmacher DS, Gordon B, Perdomo CA, F'ratt RD, et al, Open-label, multicenter, phase 3 extension study of the safety and efficacy of donepezil in patients with Alzheimer disease. Arch Neurol 2001; 58:427-433

[32] Stern RG, Mohs RC, Davidson M, Schmeidler J, Silverman J, Kramer-Ginsberg E, Searcey T, Bierer L, Davis KL, A longitudinal study of Alzheimer's disease: measurement, rate, and predictors of cognitive deterioration. Am J Psychiatry 1994; 151:390-396

[33] http://clinicaltrials.gov/ct2/show/NCT00478205

The same analysis as described above applied to galantamine pivotal data and extension did not show a decline in efficacy.[34] Furthermore, it was demonstrated that the continued good performance of galantamine patients was not due to dropout of poorly-performing patients, an analysis which we are not aware of in the case of donepezil.



Over the first two years, galantamine patients declined by fewer than 6 points on the Alzheimer's Disease Assessment Scale, cognitive portion, while donepezil-treated patients declined by more than 9 points.

Why did galantamine patients exhibit less of the expected increase in AChE levels, with a consequently smaller decline in drug efficacy than donepezil patients?

Inappropriate nocturnal cholinergic stimulation is likely to be a causative factor in stimulation of counter-regulatory AChE secretion. In an animal study, galantamine, which produces much smaller increases in AChE in humans when given twice a day, than donepezil does when given once a day, can be made to produce as much AChE elevation as donepezil when administered so it is active during the animal's rest period.[35] It is therefore desirable in humans that galantamine levels have fallen as low as possible before bedtime. This is more reliably accomplished by a long-acting preparation given at breakfast than a second immediate release pill given on a twice a day basis, or whenever the evening meal occurs, due to galantamine's 7-hour half life.

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[34] Raskind MA, Peskind ER, Truyen L, Kershaw P, Damaraju CRV, The cognitive benefits of galantamine are sustained for at least 36 months. A long-term extension trial. Arch Neurol 2004; 61:252-256

[35] Hernandez CM, Gearhart DA, Parikh V, Hohnadel EJ, Davis LW, Middlemore ML, Warsi SP, Waller JL, Terry, Jr AV, Comparison of galantamine and donepezil for effects on nerve growth factor, cholinergic markers, and memory performance in aged rats. JPET 2006; 316:679-694

Such a preparation may be expected to further reduce inappropriate nocturnal stimulation.

Researchers expected that cholinesterase inhibitors would cause increases in AChE with consequent decreases in acetylcholine and a loss of therapeutic efficacy. Galantamine, given as immediate-release twice a day, produced surprisingly less of the predicted changes than donepezil, which is active continuously due to its 70-hour half-life. The applicant believes this to be the result of the fact that even with twice a day dosing there are nocturnal periods of lowered AChE activity. The formulations of the present invention build on this.

Finally, in connection with claims 41 and 42, the examiner re-raises the question of Moorman. As explained in the responses of. September 20, 2006 and October 26, 2007, the twilight sleep referred to by Moorman is not normal sleep. It is a condition induced by scopolamine used in the past for sedation and the induction of amnesia for pain during labor and childbirth. It has nothing to do with regular sleep . A teaching that galanthamine may be used to assist recovery from this twilight sleep, teaches one nothing about whether it would be good or bad to have galanthamine in the brain during periods of normal sleep with either persons suffering from Alzheimer's disease or in anyone else.

To summarize therefore, galanthamine and the other compounds specified in the present claims (such as rivatsigmine discussed by Nordberg) are not conventional psychotropic drugs and the combination of Conte and WO or Nordberg does not therefore lead to anything set out in the present claims. Considerations of tolerability such as those discussed by Nordberg would point away from the present invention since they would encourage one to use formulations and dosage regimes that keep the level of active reasonably constant. Moorman is irrelevant because "twilight sleep" is a particular condition induced during child birth and has nothing to do with treatment of Alzheimer's disease or normal sleep of any type.

The invention as claimed is therefore not obvious and does comply with the requirements of 35 USC 103.

In view of the foregoing, it is submitted that this application should be allowed and an early action to this end is respectfully solicited.

Respectfully submitted,

JOHN RICHARDS
C/O LADAS & PARRY LLP
26 WEST 61 ST STREET
NEW YORK, NEW YORK 10023
REG. NO. 31053
TEL. NO. (212) 708-1890